Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Adrenal insufficiency: Diagnosis in patients with liver cirrhosis is difficult

Reply to the Letter to the Editor

Reply to Montagnese et al.:

We were very interested by the letter of Montagnese et al. published in this issue of the Journal of Hepatology [1]. Many recent publications led us to believe that adrenal insufficiency, assessed by serum total cortisol assays, was very common in patients with liver cirrhosis [2–7]. In fact, cortisol transport proteins (cortisol binding globulin and albumin) are often decreased in patients with cirrhosis, leading to a reduced bound fraction of cortisol, whereas free cortisol concentration, which is the active fraction of cortisol, remains unchanged. We recently showed that serum total cortisol assays (performed at 8 AM before and after a corticotropin injection) largely overestimate adrenal insufficiency prevalence in patients with cirrhosis, especially in those with serum albumin $\leqslant$25 g/L [8].

Interestingly, Montagnese and colleagues assessed the 24-h rhythm of cortisol in patients with cirrhosis using plasma free cortisol assays, avoiding the bias of the reduced cortisol transport proteins. They report that patients with Child-Pugh B/C cirrhosis have significantly lower plasma free cortisol concentrations and that their rhythm onset and offset are (not significantly) delayed compared to patients with Child-Pugh A cirrhosis. This delay could make the diagnosis of adrenal insufficiency more complicated in patients with severe cirrhosis.

In our study, we found that adrenal insufficiency assessed by salivary cortisol (an accurate reflection of free cortisol) was lower than previously reported with serum total cortisol, but not rare (8/88: 9.1%) [8]. All eight patients with adrenal insufficiency were classified as Child-Pugh C. It is unlikely that our results are partly explained by the delayed cortisol rhythm of patients with Child-Pugh B/C cirrhosis highlighted by Montagnese and colleagues. In fact, the maximal plasma free cortisol concentration seems very close to 8 AM in the study of Montagnese, which is the moment when we collected saliva and blood samples to assess cortisol concentrations. These interesting results should be confirmed by a larger study (Montagnese and colleagues included 4 patients with Child-Pugh B and two patients with Child-Pugh C) to determine if this delay has reliable consequences on the diagnosis of adrenal insufficiency in patients with cirrhosis.

Conflict of interest

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Silibinin monotherapy prevents graft infection after orthotopic liver transplantation in a patient with chronic hepatitis C

To the Editor:

We read with great interest the letter by Neumann et al. [1] on the effect of Silibinin in preventing graft infection in a patient with cirrhosis due to chronic hepatitis C (HCV). We obtained the same result in a patient treated with intravenous (i.v.) Silibinin mono-therapy (Legalon SIL®, Rottapharm-Madaus).

In 1994, the 46-year-old male patient with beta-thalassemia was first diagnosed for HCV with mixed genotype 1a/4. Both genotypes were also present upon starting silibinin treatment and on the day of OLTx. In 1998, he was treated with 5 MU interferon three times a week and weight based ribavirin. Treatment was stopped due to failure to clear the virus after 24 weeks of treatment.

In 2009, he presented with end stage liver failure (Child–Pugh stage C, MELD 20). In the mean time, he had developed insulin dependent diabetes mellitus which is treated with insulin aspartate (Novomix 30 100 E/ml, Novo Nordisk Pharma GmbH; 16 IE-0-0/day). He was listed for orthotopic liver transplantation (OLT) on the 29th of October 2009. Based on our observation of the potent antiviral effects of Silibinin [2,3] a feasibility study was discussed in the transplant setting.

Accordingly, a patient placed first on the waiting list for OLT should receive i.v. Silibinin. In this patient a donor liver became available on day 15 of Silibinin mono-therapy. The data on virus concentrations, obtained pre and after OLT, are shown in Fig. 1. Baseline virus load was low (28.800 IU/ml) and decreased on intravenous Silibinin mono-therapy to 43 IU/ml on the day of OLTx. Due to a miscommunication between our outpatient center and the OLT-team, treatment was interrupted for 2 days after OLT and virus concentration increased to 115 IU/ml. Nevertheless, HCV-RNA levels decreased after resuming Silibinin-infusions to 30 IU/ml on day 6 and became unquantifiable (<15 IU/ml) on day 10, and undetectable on day 22 after OLT. Silibinin was stopped 25 days after OLT. During 5 months of follow-up, HCV-RNA levels remained undetectable.

The surgical procedure and post-operative phase went ahead without any complications. Immunosuppressive therapy included prednisolone and cyclosporine A. Like in the patient of Neumann et al. [1] bilirubin levels increased during treatment with Silibinin to a maximum of 17.15 mg/dl (on day 3 post OLT) but decreased continuously while the patient was still on Silibinin. The higher increase of bilirubin in our patient could be due to the longer administration of Silibinin combined with the post-operative phase. Aminotransferase levels reached nearly normal values (ASAT 39 U/l, ALAT 32 U/l) 4 days after starting Silibinin-infusions but increased again after OLT and reached normal levels within 4 weeks after OLT.

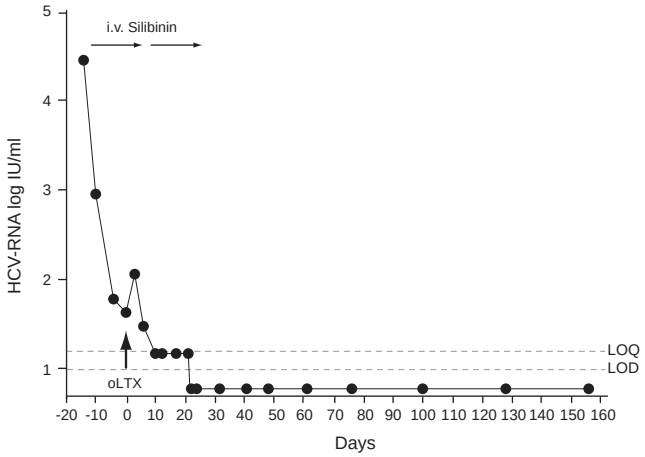

Fig. 1. HCV-kinetics during silibinin i.v. monotherapy. HCV RNA levels measured by real-time PCR (Cobas Taqman®, Roche Diagnostics, Pleasanton, CA).

While the goal to prevent graft infection was reached in both patients, the approaches were different. Neumann et al. [1] started Silibinin application 8 h after the anhepatic phase (while the viral load was 182 IU/ml). Our patient was pretreated with Silibinin for 15 days with an interruption of 2 days in the post-operative period. Previously, we have shown in a non-responders cohort that the interruption of Silibinin treatment over the week-end results in an increase in viral load [4]. The doses of Silibinin were slightly different. While Neumann et al. used a fixed dose of 1400 mg/day we applied 20 mg/kg body weight/day. The low baseline viral load may be a condition favoring the action of Silibinin.

These encouraging observations should lead to a prospective evaluation of i.v. Silibinin in this group of patients, having no medical alternatives to prevent graft infection. Studies are needed to find the best way to apply this concept in future (timing, duration, and optimal dose).

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